UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/981,020 | 10/16/2001 | Daniel S. Kohane | 0492611-0417 (MIT 8966) | 5504 |

24280 7590 09/07/2007

CHOATE, HALL & STEWART LLP
TWO INTERNATIONAL PLACE
BOSTON, MA 02110

| EXAMINER | |
|---|---|
| FUBARA, BLESSING M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1618 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 09/07/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/981,020 | KOHANE ET AL. | |
| | Examiner | Art Unit | |
| | Blessing M. Fubara | 1618 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,7-47,58-65,80,84-91 and 96-98* is/are pending in the application.

4a) Of the above claim(s) *21,22,26,29,31-36 and 38-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-20,23-25,27,28,30,37,46,47,58-65,80,84-91 and 96-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Examiner acknowledges receipt of request continued examination under 37 CFR 1.114, amendment and remarks filed 6/20/07. The amendment filed 3/26/2007 after final rejection in which claims 1, 62, 85, 86 and 90 were amended, new claim 98 was added and claims 2, 48-57, 81 and 92-95 were canceled was entered 5/4/07. Further, claims 1, 62, 85, 86 and 90 are amended in the filing of the RCE on 6/20/07. Thus claims 1, 7-47, 58-65, 80, 84-91 and 96-98 are pending and of these claims, 21, 22, 26, 29, 31-36 and 38-45 are withdrawn from consideration.

**Previous rejections that are not reiterated herein are withdrawn.**

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/20/07 has been entered.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 7, 11-14, 16-18, 23, 62, 63, 86-91 and 96-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for PLGA, albumin, muscimol, phospholipids, glucose oxidase, insulin, lactose, cellulose bupivacaine, tetraciane, lidociane,

dibucaine, mepivaciane, emulsifier and surfactant, does not reasonably provide enablement for all agents, lipids, proteins, sugars, vasodilators, anticonvulsant, diagnostic agent, prophylactic agent and synthetic polymer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is scope of enablement.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient number of the factors are discussed below for a *prima facie* case.

A. The Nature of the Invention:

The invention is drawn to compositions comprising microparticles that comprise an "agent" and a matrix comprising lipid, protein and sugar.

B. State of the prior art:

Agent is a broad term for any molecule; protein, lipid and sugar encompass more compounds than what is disclosed; vasodilator is a broad term that covers agents such as Sildenafil, nitric oxide, niacin, theobromine; protein is also a broad term that covers enzymes and antibodies other than those disclosed and claimed. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific guidance is required to enable the artisan to practice the full scope of the claimed invention. The scope of the agents, lipids, proteins, sugars, vasodilators, anticonvulsant, diagnostic agent, prophylactic agent and synthetic polymer spans compounds and molecules that are not disclosed.

C. The amount or direction or guidance presented:

Guidance is provided for PLGA, albumin, muscimol, phospholipids, glucose oxidase, insulin, lactose, cellulose bupivacaine, tetraciane, lidociane, dibucaine, mepivaciane, emulsifier and surfactants.

Therefore, in view of the lack of guidance, working examples, breadth of the claims and state of the art at the time the claimed invention was made, it would have required undue experimentation to use the invention as claimed. It is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27

USPQ2d 1662 *Ex parte Maizel.* Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)).

The above rejection may overcome by specifically reciting using Markush type language, the various compounds such as PLGA, albumin, muscimol, phospholipids, glucose oxidase, insulin, lactose, cellulose bupivacaine, tetraciane, lidociane, dibucaine, mepivaciane, emulsifier and surfactant that are the specific compounds of the broad class of compounds recited in the claims.

4. Claims 1, 7-47, 58-65, 80, 84-91 and 96-98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is new matter rejection.

The original specification does not envision microparticle composition that is not a liposome or does not comprise synthetic polymer. Applicant, for example, studied biocompatibility of particles in terms of inflammatory response and gross neural injury and mentions Yanez et al. and "touch evoked agitation" as it relates to injections of liposomes (paragraphs [0139] and [0152] of the published application). The specification as originally filed does not envision microparticles and compositions that are free of synthetic polymers that cover the broad scope of synthetic polymer. For example paragraph [0042] of the published application describes the lipid-protein-sugar-particles to optionally contain PLGA, PGA, polyesters, polyanhydrides or polyamides and these are not the only synthetic polymers.

### *Specification*

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see paragraph [0011] of the published application, for example). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

### *Claim Rejections - 35 USC § 103*

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 7, 12-20, 23-25, 27, 28, 30, 37, 46-65 and 80, 84-91 and 96-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345).

Bernstein discloses polymer matrices in the form of microparticles, wherein a lipid, or amphiphilic polymer or other hydrophobic compounds are integrated into polymeric matrix (abstract) and the matrix can be formed of synthetic or natural polymers, including proteins, such as albumin, and polysaccharides (sugars) and vasodilators (column 3, line 31 to column 4, line 22; column 6, line 56 to column 7 line 5).

Bernstein includes therapeutic and prophylactic agents among the active agents, which can be incorporated into the matrix (column 6, line 56 to column 7, line 5). The microparticles of Bernstein can be administered as powder, or formulated in tablets or capsules, or suspended in a solution with pharmaceutically acceptable carriers (column 9, lines 35-47).

The agents described in Bernstein are those that may be labeled with a fluorescent label or an enzymatic or chromatographically detectable agents (column 6, lines 61-63) are diagnostic agents. With respect to the amounts of lipid, protein and sugar claimed in claims 48-56 of the instant application, Bernstein teaches that the content of the lipid in the matrix is 0.01-60% in relation to the content of the polymer (column 6, lines 18-21) and the amount of polymer (protein) is 0.1-60% (column 4, lines 62-64). Therefore, the patent contemplates an amount of lipid up to 36%. With respect to the size of the claimed size of the microparticles claimed in claims 57-60 and 80 of the application, Bernstein discloses that the microparticles of the invention are manufactured with a diameter suitable for the intended route of administration, and discloses particles for intravascular administration having a diameter of 0.5 to 8 microns (column 2, lines 20-27). With regard to the particle size claimed in instant claim 61, Bernstein is deficient in the sense that the patent fails to disclose particles smaller than 0.5 microns. Applicant has not established comparable example in the specification to demonstrate that the

claimed small size provides some unusual and/or unexpected results. It appears to the examiner that the smaller size of particles does nothing additional to the compositions of the invention, especially in view of the teachings of the prior art, that the microparticles of the invention can be administered by any route, including administration to the lungs (column 9, lines 56-63).

With respect to the method of preparing the microparticles claimed in claim 62, Bernstein discloses that the microparticles of the invention can be produced by spray drying the polymer solution formed by dissolving the polymer (protein) and the lipid in the appropriate solvent, dispersing the active agent into the polymer solution (column 8, lines 18-33). With regard to the method of administering an agent claimed in claims 63-65 of the application, Bernstein discloses that the microparticles are combined with a pharmaceutically acceptable carrier and administered to a patient by injection into a blood vessel, subcutaneously, intramuscularly or orally (column 9, line 64 to column 10 line 6). Oral administration implies placing the microparticles in the oral cavity of the patient, thus the patent contemplates placing the microparticles in a body cavity of the patient, as claimed in claim 65 of the instant application. With respect to the ratio of lipid to protein to sugar claimed in claim 47 and also to the ratios in claims 92 and 95 of the application, it is noted that applicants have no demonstration that the ratio of lipid claimed in the instant application provides unusual/unexpected results and there is no comparable example in the specification to demonstrate that the claimed ratio of lipid provides some unusual and/or unexpected results. It appears to the examiner that the higher ratio of lipid does nothing additional to the compositions of the invention, especially in view of the teachings of the prior art, that the hydrophobic compound integrated in the polymeric matrix

modifies the diffusion of water into the microparticle and the diffusion of solubilized drug out of the matrix (column 2, lines 8-11).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Bernstein to prepare the microparticles of Bernstein with the expectation for controlled delivery of drugs.

***Response to Arguments***

9. Applicant's arguments filed 6/20/07 have been fully considered but they are not persuasive.

Applicant argues that the amendment excluding synthetic polymer from the composition overcomes Bernstein.

**Response**:

Although, Bernstein prefers the use of synthetic polymer, Bernstein contemplates using natural polymers (column 3, lines 32-37).

10. Claims 8-11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein et al. (US 6,423,345) in view of Goldenheim et al. (US 6,534,081).

The teachings of Bernstein et al. have been summarized above. The prior art is deficient in the fact, that it does not specifically include the anesthetics recited in claims 8-10 of the application and anticonvulsant agents, as claimed in claim 11, among the therapeutic agents encapsulated in the microparticles of the invention. Goldenheim provides sustained release dosage forms comprising a local anesthetic and an augmenting agent, and includes bupivacaine, dibucaine, tetracaine and lidocaine among the preferred local anesthetics used in the invention

(column 3, line 50 to column 4, line 51). Goldenheim teaches that the local anesthetic is prepared in matrices of controlled release injectable microspheres (column 5, lines 60-64), and the formulations of the invention are suitable for administration in all body spaces and cavities (column 6, lines 55-59). Goldenheim discloses formulations comprising microparticles comprising a local anesthetic, an augmenting agent and a sustained release polymer selected from synthetic polymers, proteins, polysaccharides and combinations thereof (column 7, lines 20-47). Thus, the patent provides the general teachings that local anesthetics can be delivered by microparticle compositions and specifically discloses the compounds recited in claims 8-10 of the instant application. With respect to claim 11, Goldenheim includes anticonvulsants among the augmenting agents incorporated in the compositions of the invention (column 12, lines 9-12).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Bernstein and the teachings of Goldenheim with the expectation of producing microparticles for the controlled delivery of local anesthetics and anticonvulsant drugs.

***Response to Arguments***

11. Applicant's arguments filed 6/20/07 have been fully considered but they are not persuasive.

Applicant argues that the amendment excluding synthetic polymer from the composition overcomes Bernstein.

**Response**:

Although, Bernstein prefers the use of synthetic polymer, Bernstein contemplates using natural polymers (column 3, lines 32-37).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Blessing Fubara
Patent Examiner
Tech. Center 1600